IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	Oleg Illich Epshtein *et al.*	Confirmation No:	8593
Application No:	10/522,653	Group:	1644
Filed:	January 22, 2005	Examiner:	Szperka, Michael
For:	Medicinal Agent and Method for Curing Prostate Diseases		
Customer No.:	29127		

Attorney Docket No.	75.12US1

DECLARATION UNDER 37 C.F.R. § 132 OF INVENTOR OLEG I. EPSHTEIN

1. I am Oleg I. Epshtein, a named inventor in the above-referenced U.S. patent application. I declare and affirm under the penalty of perjury under the laws of the United States that the following is true and correct based on my personal knowledge, or where not on my personal knowledge, on my information and belief.

2. I am the principal of the company "Materia Medica" which has been closely involved in the development and testing of the invention claimed in the referenced U.S. patent application. I declare as follows:

4. Homeopathic therapy and technique have been known and used since about two centuries ago. Homeopathic treatment has been founded on the principle of individualization of compounds with therapeutic activity used in ultra low doses.

5. About 20 years ago modern experimental research has shown that, independently of being tied to a specific scientific theory or explanation, ultra low doses of such compounds exhibit biological activity. It has been suggested that the observed biological activity is the result of method of preparation of the solutions: a combination of multiple consecutive dilutions and the influence of mechanical factors, all together known as a homeopathic potentiation technology. If other techniques of preparing ultra-diluted solutions are used, such as, for example, medical micropipetting, ultra diluted solutions did not exhibit biological activity.

6. In my earlier research I have established as previously unknown phenomenon with regard to the potentiated solutions. I have established that a potentiated substance, obtained from a given initial substance, has therapeutic effect on that same initial

substance. That phenomenon turned out to be true for in vitro and in vivo experiments. For example, a homeopathic ultra low dose of a known substance – ATF changes the speed of hydrolysis of ATF. An ultra low dose of LiCl affect the electroconductivity of LiCl in a solution I have proven that in vivo an ultra low dose always has some influence on the effect of the regular dose (also called a base dose) of a substance. In is principally important to emphasize that an ultra low dose of a substance influences always influences a base dose of a substance or a medicament only with respect to that same substance from which the ultra low dose was obtained.

7. During my experiments on influence of homeopathic ultra low doses on base doses, I have established that ultra low doses of antibodies influence the known effects of the antibodies. The first results were obtained with antibodies to the S-100 protein. The same model was used to discover that other antibodies in homeopathic ultra low doses cause effect on the antibodies in the traditional physiological concentrations, which demonstrates that the discovered phenomenon (a homeopathic ultra low dose of an antibody influences the effect of the same antibody in a traditional dose) is universal across different antibodies.

8. The latest developments in immunology have shown that antibodies not only play their role as anti-bacterial agents, but also are regulators of various physiological processes, similar to hormones, neuropeptides and other biologically active molecules. Presently, a small amount of antibodies (micrograms) has been discovered in blood for a large number of endogenous molecules. These existing antibodies are called natural or preexisting. It has been proven that such antibodies do not suppress the physiological activity of a molecule against which the antibodies were generated, but stabilize (modify) that molecule. At the same time antibodies retain their main property – their specificity. In the context of regulating physiological functions and processes, the antibodies specifically modify the activity of only those molecules against which the antibodies were generated.

9. The inventors' discovery is the effect of an ultra-low dosage of a substance on that substance. That includes antibodies. We have proven two principal moments:

1) used examples of ultra-low dosages of antibodies to γ-interferon, protein S100 and antibodies to opiates to demonstrate that they normalize the content of the corresponding natural antibodies in serum, which is a direct proof of the effect of the ultra low doses of antibodies on the natural antibodies.
2) it has been demonstrated during tens and tens of experiments, as well as clinical trials, that the systemic effect of ultra-low doses unidirectional with the effect of natural antibodies: potentiated antibodies do not suppress the effects known for one or another endogenous molecule, but modify it.

10. Modern anti-tumor substances based on antibodies and anti-serum based on antibodies cause therapeutic effect via direct specific bonding with a certain antigen – antibodies suppress the activity of an antigen. For the reasons not completely understood today, potentiated antibodies do not suppress the activity of endogenous regulators, but

modify them. For example, ultra low doses to a known cytokine interferon – γ increase the yield of endogenous interferon, while ultra low doses of antibodies to other cytokines do not affect the expression of γ-interferon. In another example, ultra low doses of antibodies to erytropoetin affect the erytropoetic activity, and the ultra low antibodies to granulocyte colony stimulating factor – on the granulocyte macrophage activity, which effect is of a very specific nature. Or, for example, ultra low doses of antibodies to NO-synthase do not block the activity of the enzyme, but increase its activity, which leads to the increased level of NO in tissue.

11. Nine kinds of antibodies to antigens from different groups are registered in Russia as approved medicaments.

1. Antibodies to cytokines and growth factors.
2. Antibodies to the brain specific protein S-100.
3. Antibodies to enzymes (IMPase, trypsin like protease – prostate specific antigen)
4. Antibodies to receptors (AT1 receptor angiotension II)
5. Antibodies to low molecular compounds – histamine, cholecystokinine, morphine and others.

12. All referenced medicaments have undergone the required experimental and clinical research. Despite the fact that the antigens belong to different functional groups, the ultra-low doses of their antibodies showed therapeutical activity while being safe and non-addictive. Medicaments based on ultra-low doses have therapeutic effect for different kinds of illnesses, which evidences the common mechanism of this class of medicaments. According to our results, the new phenomenon – modification of the effects of an endogenous molecule by introducing ultra low doses of antibodies to that regulator (antigen) is universal and can be used for creating and making of a much larger number of medicaments. Examples of many more experimental data confirming the stated discovery are attached to this Declaration as Appendix A (antibodies to prostate-specific antigen (PSA)).

13. Development of the medicaments based on ultra-low doses of antibodies has propelled Materia Medica, the inventor's company, to be one of the six largest manufacturers of medicines in Russia. The medicament IMPase (ultra-low doses to a prostate specific antigen) – is some of the top 20 selling medicaments in the over-the-counter segment of the market. From the start of the production 10 million doses of IMPase have been manufactured and sold. The medicament is on of the leading export product from Russia to Ukraine and Kazakhstan.

Oleg I. Epshtein

Date: January 9, 2008
Moscow, Russia

APPENDIX A

Example 1.

A study assessing efficacy and safety of ultra-low doses of antibodies to prostate-specific antigen (PSA) in treatment of benign prostatic hyperplasia (BPH) was conducted by clinical teams of Volgograd State Medical University (Volgograd, Russia), Bashkirian State Medical University (Ufa, Russia), Research Institute of Pharmacology, Tomsk Scientific Center at Siberian Department of Russian Academy of Medical Sciences (Tomsk, Russia), and Central Army and Navy Clinical Hospital number 32 (Zheleznodorozhnij, Russia). 241 males ages 40 to 75 diagnosed with BPH (stages I and II) were involved in this blind placebo-controlled study. 132 patients in the test group were given ultra-low doses of prostate-specific antigen antibodies (12C+30C+200C) in form of orally dissolving tablets (8 tablets per diem) for 16 weeks; 54 patients in the comparison group were given *Serenoa Repens* extract (320mg per diem) for 16 weeks. 55 patients in the control group received placebo tablets for 4 weeks. The severity of symptoms (difficulty urinating) and overall quality of life was assayed using IPSS questionnaire; other assays included uroflowmetry and TRUS (transrectal ultrasonography).

This study has demonstrated that administration of ultra-low doses of PSA antibodies improved the score of clinical effectiveness compared to placebo after 4 weeks of treatment. Overall IPSS score was decreased 12.9% (14.7±0.28 to 12.8±0.34) in the test group, 6.7% (13.5±0.28 to 12.6±0.38) in the placebo group. Overall quality of life improvement (expressed as decrease of quality of life index) was 13.5% (3.7±0.08 to 3.2±0.10) in the test group and 6% (3.3±0.07 to 3.1±0.09) in the placebo group. Increase of maximal flow speed of 10.8% (10.2±0.23ml/sec to 11.3±0.29ml/sec) was registered in the test group, compared to 0.8% (11.9±0.24ml/sec to 12.0±0.27ml/sec) in placebo group. After 16 weeks of treatment both the proposed agent and the *Serenoa Repens* were shown to significantly decrease the overall IPSS score by 44.6% and 43.2%, respectively. The improvement of overall quality of life was reported; quality of life index decreased in both test group and comparison group, and a more significant decrease was observed in the test group. After 16 weeks of treatment, maximal flow speed was increased by 45% in the test group and by 35.7% in the comparison group.

This study thus demonstrates efficacy and safety of the proposed agent – ultra-low doses of PSA antibodies – for treatment of benign prostatic hyperplasia.

Example 2.

A study assessing the effect of ultra-low doses of antibodies to prostate-specific antigen (PSA) on serum PSA levels in patients with benign prostatic hyperplasia (BPH) was conducted by several clinical teams. The levels of free and total PSA of 241 patients were measured (using ELISA) at the beginning and at the end of the treatment period. During 16 weeks of treatment, 132 patients in the test group were given ultra-low doses of the prostate-specific antigen antibodies (12C+30C+200C) in form of orally dissolving

tablets, 8 tablets per diem; 54 patients in the comparison group were given *Serenoa Repens* extract, 320 mg per diem; 55 patients in the control group received placebo tablets, for 4 weeks.

A statistically significant ($p<0.001$) decrease of total PSA by average of 17.6% (1.87±0.10ng/ml to 1.54±0.11ng/ml) and of free PSA by 21.7% (0.60±0.04ng/ml to 0.47±0.03ng/ml) in patients treated with ultra-low doses of PSA antibodies was demonstrated. The free-to-total serum PSA coefficient did not change and was within the normal range. Serum PSA levels of patients in both comparison group (*Serenoa Repens*) and placebo group did not change during the treatment.

This study thus demonstrates the ability of the proposed agent to decrease serum PSA levels in patients with benign prostatic hyperplasia.

Example 3.

A study assessing efficacy and safety of ultra-low doses of antibodies to prostate-specific antigen (PSA) in treatment of chronic prostatitis was conducted at Biover Medical Center (Novosibirsk, Russia). The study involved 78 patients ages 28 to 54 with chronic prostatitis (categories II and IIIa). Patients in the test group (n=32) received ultra-low doses of the prostate-specific antigen antibodies (12C+30C+200C) in form of orally dissolving tablets, 8 tablets per diem concurrently with etiopathogenetic therapy (Levofloxacin) for a period of 1 month; patients in the comparison group (n=28) received standard therapy; patients in the control group (n=18) received placebo concurrently with etiopathogenetic therapy. The effect was assayed by uroflowmetry, TRUS, manifestation of pain and spermogram (semen analysis).

It was demonstrated that ultra-low doses of PSA antibodies have a pronounced analgesic effect: none of the patient in the test group reported pain during 4 weeks of treatment; persistence of pain was reported by 32.1% of the comparison group patients and 33.2% of the placebo group patients. Proposed agent was also shown to improve uroflowmetric results (increased flow speed). In 57.4% of the treated patients proposed agents negated the toxic effect of antibacterial therapy on the spermogram values. 93.8% of treated patients evaluated the treatment's clinical effect as excellent, 6.2% - as good.

These results demonstrate the efficacy and safety of the proposed agent in treatment of chronic prostatitis.

Example 4.

A study assessing efficacy and safety of ultra-low doses of antibodies to prostate-specific antigen (PSA) in treatment of chronic vesiculitis was conducted at Irkutsk State Medical Institute for Postgraduate Training (Irkutsk, Russia). The study involved 54 patients ages 20 to 50 with deficient fertility and copulatory function, painful ejaculation, hemospermia and/or spontaneous nighttime erections. Patients in the test group (n=28) received ultra-low doses of the prostate-specific antigen antibodies (12C+30C+200C) in form of orally

dissolving tablets, 8 tablets per diem concurrently with etiopathogenetic therapy for chronic prostatitis for the period of 2 months; patients in the comparison group received standard therapy only for the same duration. The following parameters were assayed in the study: spermogram values, size and symmetricity of seminal vesicles, male copulatory function dynamic.

It was demonstrated that ultra-low doses of PSA antibodies improved spermogram values in 82.1% of treated patients; in contrast, spermogram values have deteriorated in 65.3% of the patients in the comparison group. Symmetricity and homogeneity of the seminal vesicles improved in 78.6% of the test group patients and only in 19.3% of the patients in the comparison group. The treatment was shown to improve copulatory function with statistical significance; an average of 50% increase in copulatory function score was recorded in treated patients, compared to 26.7% increase in the comparison group. None of the treated patients have reported painful ejaculation, hemospermia and/or spontaneous nighttime erections for the 2-month period of the treatment; the symptoms persisted in 53.8% of the comparison group patients.

Thus efficacy and safety of ultra-low doses of PSA antibodies in treatment of chronic vesiculitis is shown in this study.

Example 5.

A study of effect of ultra-low doses of antibodies to prostate-specific antigen (PSA) on prostate morphology and function in rats with chronic prostate inflammation was conducted at Research Institute of Pharmacology, Tomsk Scientific Center at Siberian Department of Russian Academy of Medical Sciences (Tomsk, Russia). 56 male white rats (body mass 250g) were anesthetized with ether and their prostates were stitched with silk floss (to induce inflammation). 1 month after this procedure, proposed agent (ultra-low doses of PSA antibodies) was administered intragastrically to test group animals (1.5ml per animal daily) for 45 days; distilled water was administered to control group animals. 2.5 month after the initial procedure prostate structural elements and Zn ion content were assayed.

It was shown with statistical significance that the area of the secretory epithelium of prostate acini was increased in the treated animals (16.6±1.0 to 19.2±0.5); the relative area of connective tissue was decreased. The concentration of Zn ions in the ventral prostate lobe was also significantly increased compared to control – 0.96±0.06mg/100g to 2.09±0.02mg/100g.

This study demonstrates that administration of the proposed agent prevents atrophy and sclerotic processes of the prostate, and increases Zn ion content.

Example 6.

The following study of the effect of ultra-low doses of antibodies to prostate-specific antigen (PSA) on hormone-induces prostate inflammation in rats was conducted at

Research Institute of Pharmacology, Tomsk Scientific Center at Siberian Department of Russian Academy of Medical Sciences (Tomsk, Russia). 80 male rats of unspecified lineage of late reproductive age (body mass 450-500g) were divided into 4 groups (20 animals each) and treated as follows: Group 1 – animals received sulpiride (administered into the abdominal cavity, 40mg/kg daily) and *Serenoa Repens* (intragastrically, 50mg/kg daily); Group 2 – animals received sulpiride (administered into the abdominal cavity, 40mg/kg daily) and proposed agent (intragastrically, 5ml/kg daily); Group 3 - animals received sulpiride (administered into the abdominal cavity, 40mg/kg daily); Group 4 - animals received sulpiride (administered into the abdominal cavity, 40mg/kg daily) and distilled water. After 60 days of treatment the following were assayed: total mass of the prostate, weight coefficients of its anterior, lateral and posterior lobes, histology of the lateral lobe.

It was shown that after 60 days of treatment the total mass and the weight coefficients of lateral and posterior lobes of prostates of the control animals reproducibly increased compared to intact animals. Proposed agent, as well as *Serenoa Repens*, inhibited development of sulpiride-induced prostate hyperplasia in rats: weight coefficients of anterior, lateral and posterior prostate lobes in groups receiving the proposed agent and *Serenoa Repens* were reproducibly lower than those of control group animal receiving distilled water. The proposed agent was more effective that *Serenoa Repens* in retarding the increase of the weight coefficient of the lateral lobe in rats exposed to sulpiride: after 60 days of treatment, average lateral lobe weight coefficient of animals treated with proposed agent was 1.7 times lower than of those treated with *Serenoa Repens* (0.07 ± 0.01 mg/g vs. 0.12 ± 0.01 mg/g; $p<0.05$).

Thus, it is shown that administration of the proposed agent prevents development of prostate hyperplasia and decreases appearance of pathology in prostatic tissues of animals with hormone-induced prostate inflammation stimulated by sulpiride.